Functional assessment of long-term deficits in rodent models of traumatic brain injury.

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Public Summary:
Traumatic brain injury (TBI) ranks as the leading cause of mortality and disability in the young population worldwide. The annual US incidence of TBI in the general population is estimated at 1.7 million per year, with an estimated financial burden in excess of US$75 billion a year in the USA alone. Despite the prevalence and cost of TBI to individuals and society, no treatments have passed clinical trial to clinical implementation. The rapid expansion of stem cell research and technology offers an alternative to traditional pharmacological approaches targeting acute neuroprotection. However, preclinical testing of these approaches depends on the selection and characterization of appropriate animal models. In this article we consider the underlying pathophysiology for the focal and diffuse TBI subtypes, discuss the existing preclinical TBI models and functional outcome tasks used for assessment of injury and recovery, identify criteria particular to preclinical animal models of TBI in which stem cell therapies can be tested for safety and efficacy, and review these criteria in the context of the existing TBI literature. We suggest that 2 months post-TBI is the minimum period needed to evaluate human cell transplant efficacy and safety. Comprehensive review of the published TBI literature revealed that only 32% of rodent TBI papers evaluated functional outcome >/=1 month post-TBI, and only 10% evaluated functional outcomes >/=2 months post-TBI. Not all published papers that evaluated functional deficits at a minimum of 2 months post-TBI reported deficits; hence, only 8.6% of overall TBI papers captured in this review demonstrated functional deficits at 2 months or more postinjury. A 2-month survival and assessment period would allow sufficient time for differentiation and integration of human neural stem cells with the host. Critically, while trophic effects might be observed at earlier time points, it will also be important to demonstrate the sustainability of such an effect, supporting the importance of an extended period of in vivo observation. Furthermore, regulatory bodies will likely require at least 6 months survival post-transplantation for assessment of toxicology/safety, particularly in the context of assessing cell abnormalities.

Scientific Abstract:
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